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BONE MARROW AND STEM CELL TRANSPLANTATION

Bone marrow transplantation is the generic term used to describe the collection and transplantation of hematopoietic stem cells. The procedure is usually carried out for one of two purposes: (1) to replace an abnormal but nonmalignant lymphohematopoietic system with one from a normal donor, or (2) to treat malignancy by allowing the administration of higher doses of myelosuppressive therapy than would otherwise be possible. The use of bone marrow transplantation has been steadily increasing, both because of the its demonstrated effectiveness in selected diseases and because of increasing availability of donors. The International Bone Marrow Transplant Registry estimates that about 50,000 transplants were performed during 1999.

THE HEMATOPOIETIC STEM CELL

Several features of the hematopoietic stem cell make bone marrow transplantation clinically feasible, including its remarkable regenerative capacity, its ability to home to the marrow space following intravenous injection, and the ability of the stem cell to be cryopreserved. Transplantation of a single stem cell can replace the entire lymphohematopoietic system of an adult mouse. In humans, transplantation of a few percent of a donor's bone marrow volume regularly results in complete and sustained replacement of the recipient's entire lymphohematopoietic system, including all red cells, granulocytes, B and T lymphocytes, and platelets, as well as cells comprising the fixed macrophage population, including Kupffer cells of the liver, pulmonary alveolar macrophages, osteoclasts, Langerhans cells of the skin, and brain microglial cells. The ability of the hematopoietic stem cell to home to the marrow following intravenous injection is mediated, at least in part, by the interaction of specific cell molecules, termed *selectins*, on bone marrow endothelial cells with their unique ligands, termed *integrins*, on early hematopoietic cells. Human hematopoietic stem cells can survive freezing and thawing with little, if any, damage, making it possible to remove and store a portion of the patient's own bone marrow for later reinfusion following treatment of the patient with high-dose myelotoxic therapy.

CATEGORIES OF BONE MARROW TRANSPLANTATION

Bone marrow transplantation can be described according to the relationship between the patient and the donor and by the anatomic source of stem cells. In approximately 1% of cases, patients have identical twins who can serve as donors. Syngeneic donors represent the best source of stem cells; unlike allogeneic donors, there is no risk of graft-versus-host disease (GVHD) and, unlike use of autologous marrow, there is no risk that the stem cells are contaminated with tumor cells.

Allogeneic transplantation involves a donor and recipient who are not immunologically identical. Following allogeneic transplantation immune cells transplanted with the marrow or developing from it can react against the patient, causing GVHD. Alternatively, if the immunosuppressive preparative regimen used to treat the patient before transplant is inadequate, immunocompetent cells of the patient can cause graft rejection. The risks of these complications are greatly influenced by the degree of matching between donor and recipient for antigens encoded by genes of the major histocompatibility complex.

The human leukocyte antigen (HLA) molecules are responsible for binding antigenic proteins and presenting them to T cells. The antigens presented by HLA molecules may derive from exogenous sources (e.g., during active infections) or may be endogenous proteins produced by the cell. If individuals are not matched for HLA, T cells from one individual will react strongly to the mismatched HLA, or "major antigens," of the second. Even if the individuals are HLA-matched, the T cells of the donor may react to differing endogenous, or "minor antigens," presented by the HLA of the recipient. Reactions to minor antigens tend to be less vigorous. The genes of major relevance to transplantation include HLA-A, -B, -C, and -D; they are closely linked and therefore tend to be inherited as haplotypes, with only rare crossovers between them. Thus, the odds that any one full sibling will match a patient are one in four, and the probability that the patient has an HLA-identical sibling is $1 - (0.75)^n$ where n equals the number of siblings.

With current techniques, the risk of graft rejection is 1 to 3%, and the risk of severe, life-threatening acute GVHD is approximately 15% following transplantation between HLA-identical siblings. The incidence of graft rejection and GVHD increases progressively with the use of family member donors mismatched for one, two, or three antigens. While survival following a one-antigen mismatched transplant is not markedly altered, survival following two- or three-antigen mismatched transplants is significantly impaired, and such transplants should only be performed as part of clinical trials.

The formation of the National Marrow Donor Program has allowed for the identification of HLA-matched unrelated donors for many patients. The genes encoding HLA antigens are highly polymorphic, and thus the odds of any two unrelated individuals being HLA-identical are extremely low, somewhat less than 1 in 10,000. However, by identifying and typing >3 million volunteer donors, HLA-matched donors now can found for approximately 50% of patients for whom a search is initiated. It takes, on average, 3 to 4 months to complete a search and schedule and initiate an unrelated donor transplant. Results so far suggest that GVHD is somewhat increased and survival somewhat poorer with such donors than with HLA-matched siblings.

Autologous transplantation involves the removal and storage of the patient's own stem cells with subsequent reinfusion after the patient receives high-dose myeloablative therapy. Unlike allogeneic transplantation, there is no risk of GVHD or graft rejection with autologous transplantation. On the other hand, autologous transplantation lacks a graft-versus-tumor effect, and the autologous stem cell product can be contaminated with tumor cells that could lead to relapse. A variety of techniques have been developed to "purge" autologous products of tumor cells. Some use antibodies directed at tumor-associated antigens plus complement, antibodies linked to toxins, or antibodies conjugated to immunomagnetic beads. In vitro incubation with certain chemotherapeutic agents such as 4-hydroperoxycyclophosphamide and long-term culture of bone marrow has also been shown to diminish tumor cell numbers in stem cell products. Another technique is positive

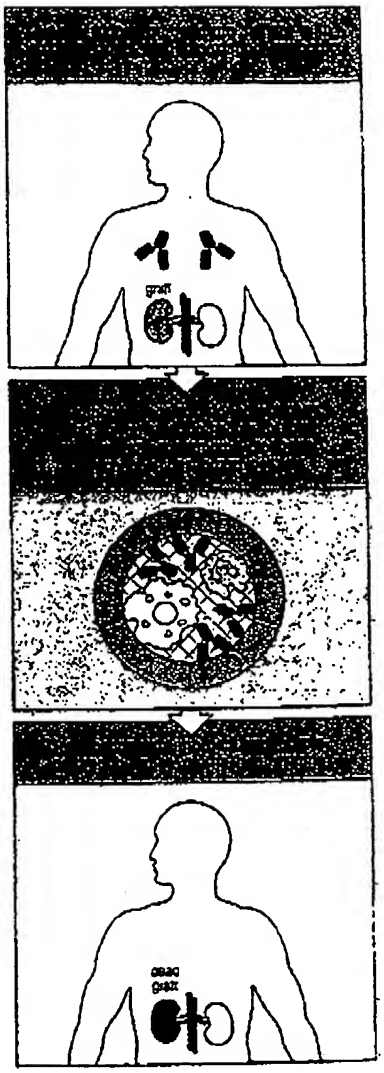

Fig. 13.27 **Preexisting antibody against donor graft antigens can cause hyperacute graft rejection.** In some cases, recipients already have antibodies to donor antigens, which are often blood group antigens. When the donor organ is grafted into such recipients, these antibodies bind to vascular endothelium in the graft, initiating the complement and clotting cascades. Blood vessels in the graft become obstructed by clots and leak, causing hemorrhage of blood into the graft. This becomes engorged and turns purple from the presence of deoxygenated blood.

is exacerbated in xenografts because complement-regulatory proteins such as CD59, DAF (CD55), and MCP (CD46) (see Section 2-14) work less efficiently across a species barrier: the complement-regulatory proteins of the xenogeneic endothelial cells cannot protect them from attack by human complement. A recent step toward xenotransplantation has been the development of transgenic pigs expressing human DAF. Preliminary experiments have shown prolonged survival of organs transplanted from these pigs into recipient cynomolgus monkeys, under cover of heavy immunosuppression. However, hyperacute rejection is only the first barrier faced by a xenotransplanted organ. The T lymphocyte-mediated graft rejection mechanisms might be extremely difficult to overcome with present immunosuppressive regimes.

13-21 The converse of graft rejection is graft-versus-host disease.

Allogeneic bone marrow transplantation is a successful therapy for some tumors derived from bone marrow precursors, such as certain leukemias and lymphomas. It may also be successful in the treatment of some primary immunodeficiency diseases (see Chapter 11) and inherited bone marrow diseases, such as the severe forms of thalassemia. In leukemia therapy, the recipient's bone marrow, the source of the leukemia, must first be destroyed by aggressive cytotoxic chemotherapy. One of the major complications of allogeneic bone marrow transplantation is graft-versus-host disease (GVHD), in which mature donor T cells that contaminate the allogeneic bone marrow recognize the tissues of the recipient as foreign, causing a severe inflammatory disease characterized by rashes, diarrhea, and pneumonitis. Graft-versus-host disease occurs not only when there is a mismatch of a major MHC class I or class II antigen but also in the context of disparities between minor H antigens. Graft-versus-host disease is a common complication in recipients of bone marrow transplants from HLA-identical siblings, who typically differ from each other in many polymorphic proteins encoded by genes unlinked to the MHC.

The presence of alloreactive T cells can easily be demonstrated experimentally by the mixed lymphocyte reaction (MLR), in which lymphocytes from a potential donor are mixed with irradiated lymphocytes from the potential recipient. If the donor lymphocytes contain alloreactive T cells, these will respond by cell division (Fig. 13.28). The MLR is sometimes used in the selection of donors for bone marrow transplants, when the lowest possible alloreactive response is essential. However, the limitation of the MLR in selection of bone marrow donors is that the test does not accurately quantitate alloreactive T cells. A more accurate test is a version of the limiting-dilution assay (see Appendix I, Section A-25), which precisely counts the frequency of alloreactive T cells.

Although graft-versus-host disease is usually harmful to the recipient of a bone marrow transplant, there can be some beneficial effects. Some of the therapeutic effect of bone marrow transplantation for leukemia can be due to a graft-versus-leukemia effect, in which the allogeneic bone marrow recognizes

Graft-Versus-Host Disease

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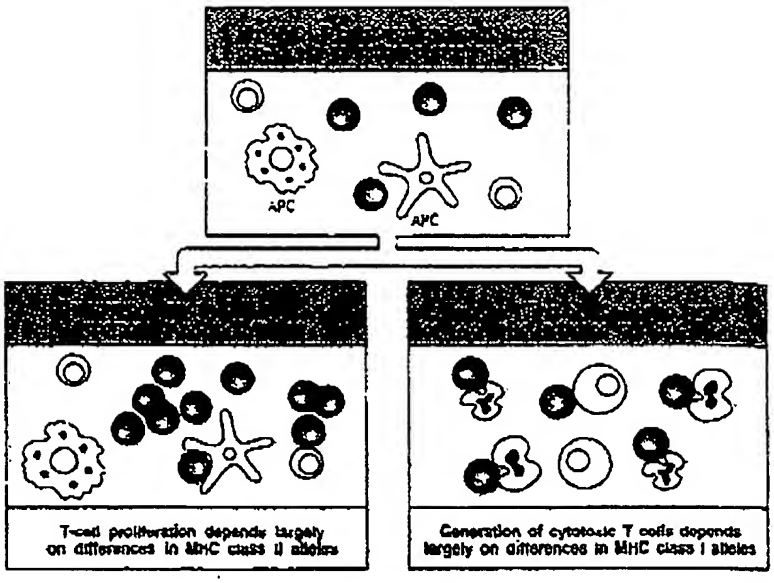

Fig. 13.28 The mixed lymphocyte reaction (MLR) can be used to detect histoincompatibility. Lymphocytes from the two individuals who are to be tested for compatibility are isolated from peripheral blood. The cells from one person (yellow), which will also contain antigen-presenting cells, are either irradiated or treated with mitomycin C, they will act as stimulator cells but cannot now respond by DNA synthesis and cell division to antigenic stimulation by the other person's cells. The cells from the two individuals are then mixed (top panel). If the unirradiated lymphocytes (the responders, blue) contain alloreactive T cells, these will be stimulated to proliferate and differentiate to effector cells. Between 3 and 7 days after mixing, the culture is assessed for T-cell proliferation (bottom left panel), which is mainly the result of CD4 T cells recognizing differences in MHC class II molecules, and for the generation of activated cytotoxic T cells (bottom right panel), which respond to differences in MHC class I molecules.

minor H antigens or tumor-specific antigens expressed by the leukemic cells, leading the donor cells to kill the leukemic cells. One such minor H antigen, HB-1, is a B-cell lineage marker that is expressed by acute lymphoblastic leukemia cells, which are B-lineage cells, and by B lymphocytes transformed with Epstein–Barr virus (EBV). One of the treatment options for suppressing the development of graft-versus-host disease is the elimination of mature T cells from the donor bone marrow *in vitro* before transplantation, thereby removing alloreactive T cells. Those T cells that subsequently mature from the donor marrow *in vivo* in the recipient are tolerant to the recipient's antigens. Although the elimination of graft-versus-host disease has benefits for the patient, there is an increase in the risk of leukemic relapse, which provides strong evidence in support of the graft-versus-leukemia effect.

13-22 Chronic organ rejection is caused by inflammatory vascular injury to the graft.

The success of modern immunosuppression means that approximately 85% of cadaveric kidney grafts are still functioning a year after transplantation. However, there has been no improvement in rates of long-term graft survival: the half-life for functional survival of renal allografts remains about 8 years. The major cause of late organ failure is chronic rejection, characterized by concentric arteriosclerosis of graft blood vessels, accompanied by glomerular and tubular fibrosis and atrophy.

Mechanisms that contribute to chronic rejection can be divided into those due to alloreactivity and those due to other pathways, and into early and late events after transplantation. Alloreactivity may occur days and weeks after transplantation and cause acute graft rejection. Alloreactive responses may also occur months to years after transplantation, and be associated with clinically hard-to-detect gradual loss of graft function. Other important causes of chronic graft rejection include ischemia–reperfusion injury, which occurs at the time of grafting but may have late adverse effects on the grafted organ, and later-developing adverse factors such as chronic cyclosporin toxicity or cytomegalovirus infection.

Infiltration of the graft vessels and tissues by macrophages, followed by scarring, are prominent histological features of late graft rejection. A model of injury has been developed in which alloreactive T cells infiltrating the graft secrete cytokines that stimulate the expression of endothelial adhesion molecules and also secrete chemokines such as RANTES (see Fig. 2.33), which attracts monocytes that mature into macrophages in the graft. A second phase of chronic inflammation then supervenes, dominated by macrophage products including interleukin (IL)-1, TNF-α and the chemokine MCP, which leads to further macrophage recruitment. These mediators conspire to cause chronic inflammation and scarring, which eventually leads to irreversible organ failure. Animal models of chronic rejection also show that alloreactive IgG antibodies may induce accelerated atherosclerosis in transplanted solid organs.

13-23 A variety of organs are transplanted routinely in clinical medicine.

Although the immune response makes organ transplantation difficult, there are few alternative therapies for organ failure. Three major advances have made it possible to use organ transplantation routinely in the clinic. First, the technical skill to carry out organ replacement surgery has been mastered by many people. Second, networks of transplantation centers have been organized to ensure that the few healthy organs that are available are HLA-typed and so matched with the most suitable recipient. Third, the use of powerful immunosuppressive drugs, especially cyclosporin A and FK-506, known as tacrolimus, to inhibit T-cell activation (see Chapter 14), has increased graft survival rates dramatically. The different organs that are transplanted in the clinic are listed in Fig. 13.29. Some of these operations are performed routinely with a very high success rate. By far the most frequently transplanted solid organ is the kidney, the organ first successfully transplanted between identical twins in the 1950s. Transplantation of the cornea is even more frequent; this tissue is a special case, as it is not vascularized, and corneal grafts between unrelated people are usually successful even without immunosuppression.

Kidney	80–90%	13,429 (12,483)
Liver	40–50%	4698
Heart	70%	2234 (2185)
Lung	30–40%	934 (885)
Cornea	~70%	~40,000†
Bone marrow	60%	23,500‡

Fig. 13.29 Tissues commonly transplanted in clinical medicine. All grafts except corneal and some bone marrow grafts require long-term immunosuppression. The number of organ grafts performed in the United States in 1999 is shown. Figures in brackets are for the organ alone, while the total figure includes combination transplants, e.g., heart and lungs. *The 5-year survival values are an average, closer matching between donor and recipient generally gives better survival. Data courtesy of United Network for Organ Sharing. † Data for 2000 courtesy of National Eye Institute ‡ Data for 1998 courtesy of International Bone Marrow Transplant Registry.

There are, however, many problems other than graft rejection associated with organ transplantation. First, donor organs are difficult to obtain; this is especially a problem when the organ involved is a vital one, such as the heart or liver. Second, the disease that destroyed the patient's organ might also destroy the graft. Third, the immunosuppression required to prevent graft rejection increases the risk of cancer and infection. Finally, the procedure is very costly. All of these problems need to be addressed before clinical transplantation can become commonplace. The problems most amenable to scientific solution are the development of more effective means of immunosuppression, the induction of graft-specific tolerance, and the development of xenografts as a practical solution to organ availability.

13-24 The fetus is an allograft that is tolerated repeatedly.

All of the transplants discussed so far are artefacts of modern medical technology. However, one tissue that is repeatedly grafted and repeatedly tolerated is the mammalian fetus. The fetus carries paternal MHC and minor H antigens that differ from those of the mother (Fig. 13.30), and yet a mother can successfully bear many children expressing the same nonself MHC proteins derived from the father. The mysterious lack of rejection of the fetus has puzzled generations of reproductive immunologists and no comprehensive explanation has yet emerged. One problem is that acceptance of the fetal allograft is so much the norm that it is difficult to study the mechanism that prevents rejection; if the mechanism for rejecting the fetus is rarely activated, how can one analyze the mechanisms that control it?

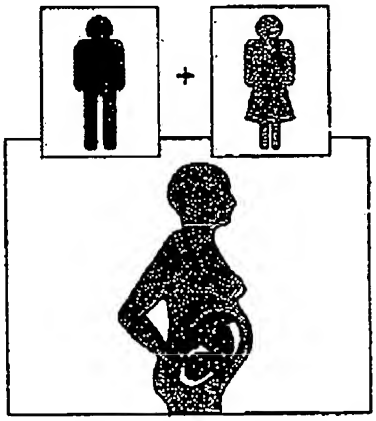

Fig. 13.30 The fetus is an allograft that is not rejected. Although the fetus carries MHC molecules derived from the father, and other foreign antigens, it is not rejected. Even when the mother bears several children to the same father, no sign of immunological rejection is seen.

Clinical Laboratory Medicine

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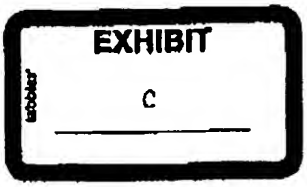

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varieties of antibody found in the patient's serum during the pretransplant antibody screening. Thus the importance of pretransplant screening cannot be overemphasized. This procedure allows a detailed and accurate assessment of the antibody repertoire carried by the patient in a relatively leisurely manner rather than under the stresses associated with a cadaveric donor organ harvest and the overzealous anticipation of a possible transplant.

When using a cadaveric donor the lymphocytes of choice are prepared from excised lymph nodes or a section of spleen obtained in conjunction with organ harvesting. The nodes should be kept moist after their removal and during delivery to the laboratory. Some workers advocate the use of peripheral blood from the potential donor in order to save time. This is a debatable point. The peripheral blood cells of patients who have been kept on life support systems may be unsuitable for use in the cytotoxicity test for a number of reasons, including the effects of antemortem steroids administered to reduce cerebral edema. Consequently, uninterpretable results may often be obtained, requiring the tests to be repeated. Thus, little time is saved and the expense of duplicate work is incurred.

It is best to perform the cross-match using pure T cells as targets (20). This is good practice, since anti-HLA class I antibodies are the most frequently encountered and the most clinically significant. In addition, many types of patients such as those with lupus erythematosus, certain diabetics, and others often demonstrate nonspecific autoreactivity. This is most frequently directed against B cells and seems to have no clinical significance. If mixtures of T and B cells are used in the cross-match with the sera of such patients, they would give a positive result. Therefore a transplant would be denied because of a false-positive reaction.

In contrast to nonspecific B-cell antibodies, those directed against class II HLA antigens are of definite clinical relevance. Pretransplant antibody screens should be designed for their detection and identification. In addition, cross-matches with the serum of patients containing such antibodies should be performed using suspensions of B cells.

Flow cytometry is currently being investigated as a sensitive adjunct for performing cross-matches (21). In addition to being extremely sensitive, this method has the advantage of being able to dissect the reaction between the serum of the recipient and the cells of the donor with respect to the cell types involved (T or B), the immunoglobulin class (IgM or IgG), and the quantity of antibody being bound. Such information allows for a more sophisticated judgment to be made as to the suitability of a particular donor for a given recipient. Furthermore, the technique has the advantage of being complement independent. Therefore it is capable of detecting noncomplement binding antibodies as well as avoiding some of the pitfalls associated with complement binding reactions. However, it is not entirely free of disadvantages. It is time consuming, requires expensive equipment, and demands highly skilled operators and expertise in interpretation.

TRANSPLANTATION—BONE MARROW

In patients who have never been previously immunized to HLA antigens, the single most important consideration in the grafting of bone marrow is the prevention of a reaction of the engrafted cells against the recipient. Immunologically competent donor cells reacting with recipient tissues can lead to a serious disorder known as graft versus host disease (GVH). Most patients who require a bone marrow transplant have a nonfunctioning immune system because of their underlying disease or therapy. If this is not the case, deliberate immunologic incompetence is induced by cytoreductive chemotherapy and/or irradiation prior to transplantation. Under these conditions, the recipient cannot respond easily to foreign antigens in the donor and therefore the problem of graft rejection is not as important as in other forms of transplantation. However, since the donor cells have full immunologic potential, they can recognize the recipient antigens and react against them. Total identity for all antigens of the major histocompatibility complex appears to be an important factor in keeping the GVH reaction to a minimum. For this reason, the assessment of nonreactivity between donor and host as defined by the mixed leukocyte culture (MLC) is a paramount consideration prior to transplantation. The early attempts at marrow grafting were carried out using HLA-identical siblings as donors. Further clinical trials indicated that sibling donors who differed from the recipient by only one or two HLA antigens could be used successfully. Sibling donors who demonstrated class II identity and class I mismatch in part of a haplotype due to recombination could be used as donors. Current data indicate that unrelated donors may be used with some degree of success if they are well matched for HLA. The degree of permissible mismatch among unrelated donor-recipient combinations is being investigated (22).

Large numbers of HLA-typed potential donors of bone marrow are being developed in England, the United States, and elsewhere to satisfy the needs of patients lacking appropriate siblings. The selection of an unrelated donor is made through a comparison of the total HLA type. The cells of the potential donor identified from a donor file by such a comparison are

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